## REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the above amendment. The attached page is captioned **"Version with markings to show changes made."**

Support for the amendments to claims 1 and 4 are found at least in the recitation of "drying" in claim 4, on the first full paragraph on pages 34 and 41, and in claims 3 and 20 as originally filed. Claims 3 and 20 have been amended to be consistent with the amendments in claim 1.

Claim 12 has been amended to correct a clerical error.

Claim 15 has been amended to define a specific "benzoporphyrin derivative" where possible. The particular BPDs recited in the claim are known by the identifiers used and are disclosed in the specification at least on page 30-31 of the specification and the references cited therein. They are photosensitizing compounds known in the art and the introduction of structural representations of the compounds is not believed to be necessary.

Claims 17 and 22-25 have been amended to correct clerical errors.

Claim 18 has been amended to correct its dependency.

Claim 21 has been amended to utilize alternate language for the same subject matter.

Claims 26-28 have been amended to be consistent with claim 4 as amended.

The amendment to claim 1 to recite "block copolymer" has been made for reasons related to business considerations and commercially contemplated embodiments of the invention rather than in acquiescence to any position set forth in the Office Action. Applicants reserve the right to pursue the claim as originally filed in a continuing application.

No new matter has been introduced, and entry of the amendments is respectfully requested.

***Rejections under 35 U.S.C. § 112***

Claims 1-30 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly non-enabled for the scope encompassing exo-supports. Applicants have carefully reviewed the statement of the rejection and believe that it is based on the view that exo-supports may not allow access to the components contained therein. Applicants traverse for the following reasons.

As an initial matter, the inclusion of claims 2, 7, and 16-18 in the instant rejection appears to be misplaced. These claims expressly recite the use of endo-supports and are thus not believed to be within the scope of the alleged non-enablement asserted in the instant rejection. Therefore, the inclusion of these claims in the instant rejection is believed to be in error.

With respect to claims 1, 3-6, 8-15 and 19-30, Applicants respectfully point out that the specification discusses exo-supports in detail at least on page 7, line 21, through page 9 and pages 40-41. Within these passages, the use of exo-supports is detailed, including a discussion of various biopolymers that may be used (see, for example, bottom of page 8) as well as how they may be used (see, for example, page 40, lines 7-8).

The discussion also includes the description of exo-supports as hydratable and/or soluble to permit access to, or release of, the encapsulated material. Thus in cases of encapsulated material that is to be hydrated with water, the skilled artisan would immediately recognize that hydratable or water soluble exo-support may be used. This is supported by Madden (USP 5,389,378) as cited in the Office Action, which discloses the use of capsules as an exo-support. Alternatively, and if a non-hydratable or water insoluble exo-support is used, then the encapsulation would be "partial" such that hydration or solvation of the encapsulated material may occur.

Additionally, no more than routine and repetitive experimentation is needed by the skilled artisan to make and use compositions comprising an exo-support as encompassed by the claims and disclosed in the instant application.

In light of the above points as well as no evidence of excessive unpredictability to make and use the claimed invention with respect to exo-support containing compositions, Applicants respectfully submit that no *prima facie* case of undue experimentation or non-enablement has been presented. Therefore, the instant rejection appears to be misplaced, and may be properly withdrawn.

Claims 3, 12, 15, 21-25 and 27 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicants have carefully reviewed the statement of the rejection and believe that the claims are definite for the following reasons.

The language of claims 3 and 20 have been incorporated into claim 1 as amended above along with the deletion of "liposomes". Accordingly, no inconsistency between the recitation of "liposomes" and "micelles" remains in claim 20-25 and 27.

The parentheses in claim 12 have been removed. The parentheses in claims 24 and 25 denote alternative nomenclature for the poloxamer compounds recited in the claims. While they may be removed without altering the subject matter of the claims, Applicants believe that they increase clarity by providing the alternative nomenclature by which the poloxamers are known.

The terms in claims 15, 24 and 25 are the identifiers of the specific compounds as they are known in the art. They are not abbreviations or acronyms that may be spelled out in their entirety.

Claim 18 has been amended to correct its dependency. Non-hydratable solid supports would remain a solid after hydration and may be readily removed by any appropriate technique known in the art, including centrifugation or filtration.

Claim 21 has been amended to remove the recitation of "type" without altering the scope of the claim.

Applicants respectfully submit that this rejection has been obviated and may be withdrawn.

***Prior art rejection under 35 U.S.C. § 102(b)***

Claims 1-16, 19 and 26-30 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Madden (USP 5,389,378). Applicants have carefully reviewed the statement of the rejection and the cited prior art and traverse for the following reasons.

Applicants respectfully note that the instant rejection failed to present a *prima facie* case of anticipation of claim 1 as originally filed because Madden entirely fails to disclose a "carrier agent" as recited in the claim. Therefore, no claim amendment was necessary to obviate this rejection, and the instant rejection should be withdrawn on this basis alone.

Madden also fails to teach, suggest or otherwise indicate a composition comprising a block copolymer or capable of forming micelles upon hydration (the terms are not even used in the patent), to which claims 1-16, 19, 26-28 and 30 are now directed. Accordingly, Madden fails to anticipate the claims and withdrawal of the instant rejection is respectfully requested.

Claims 1-17 and 26-30 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Desai et al. (USP 6,074,666). Applicants have carefully reviewed the statement of the rejection and the cited prior art and traverse for the following reasons.

As with Madden above, Applicants respectfully note that the instant rejection fails to present a *prima facie* case of anticipation of claim 1 as originally filed because Desai et al. entirely fail to disclose a "carrier agent" as recited in the claim. Therefore, no claim amendment was necessary to obviate this rejection, and the instant rejection should be withdrawn on this basis alone.

Desai et al. also fail to teach, suggest or otherwise indicate a composition comprising a block copolymer or capable of forming micelles upon hydration (the terms are not even used in the patent), to which claims 1-17, 26-28 and 30 are now directed. Accordingly, Desai et al. fail to anticipate the claims and withdrawal of the instant rejection is respectfully requested.

***Prior art rejection under 35 U.S.C. § 103***

Claims 1-20 and 27-30 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Lentini (USP 5,885,557) or Young et al. (USP 6,375,930) in light of Unger (USP 6,028,066). Applicants have carefully reviewed the statement of the rejection as well as the cited references and understand the rejection to be based upon Lentini or Young et al. in the alternative and each in combination with Unger. Applicants respectfully traverse as follows.

The statement asserts that Lentini and Young et al. both do not teach "the inclusion of a saccharide such as trehalose and polymers such as PEG and polyvinyl pyrrolidone". Applicants are unsure whether these deficiencies are meant to be directed to a "carrier agent" and a solid (endo- or exo-) support as recited in the originally filed claims. If so, Applicants agree that neither of these references teach or suggest a "carrier agent" or a solid (endo- or exo-) support physically associated with a mixture of a photosensitizer and a "carrier agent".

Unger, however, fails to correct these deficiencies. The description of "additives" at column 79, lines 45-57, in Unger are insufficient even though glucose, trehalose, polyvinyl pyrrolidone and PEG are included. This follows because these "additives" are used to "prevent agglutination or fusion of the lipids and/or vesicles" as opposed to being the carrier agent or the

solid support as recited in the originally filed claims. As the Examiner is no doubt aware, the disclosed invention relates to the combination of a photosensitizer with a carrier agent to form a complex that is associated with a solid support. Mere inclusion of small amounts of glucose or trehalose as an additive to prevent agglutination is not the same as using it as a solid support as recited in claims 9 and 10. Similarly, mere inclusion of small amounts of polyvinyl pyrrolidone or PEG as an additive to prevent agglutination is not the same as using it as a carrier agent as recited in the claims.

Therefore, all the limitations of the claims as originally filed were not disclosed or suggested in the cited references. No *prima facie* case of obviousness was presented, and no claim amendment was necessary to obviate this rejection. The instant rejection should be withdrawn on this basis alone.

The lack of any teaching of a solid support, whether endo- or exo-, is also sufficient to demonstrate that no *prima facie* case of obviousness is presented for the claims as amended above.

Applicants note, however, that claim 1 has been amended to recite "block copolymer carrier agent", present in claim 20 as originally filed. None of the cited references disclose or suggest the use of a block copolymer as a carrier agent. Unger is the only one of these three references which even mentions the term "poloxamer" in column 40, lines 50-55. But this is in the context of using it as an "emulsifying and/or solublizing agent" as opposed to the carrier agent *per se*. Evidence that the poloxamers were not used as the carrier agent is present in column 50, lines 32-63, which details the use of lipids as the carrier agent to form vesicles and the use of a poloxamer as an additive. There is also no teaching or indication that a combination of only photosensitizer and block copolymer as a carrier agent is sufficient to result in the production of micelles upon hydration.

In light of the above distinctions between the cited references and the claimed invention, Applicants respectfully request the withdrawal of the rejection.

Claims 21-26 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Lentini (USP 5,885,557) or Young et al. (USP 6,375,930) in combination with Unger (USP 6,028,066) and in light of Kataoka et al. (*J. Controlled Med.* 24:119-132, 1993). Applicants have carefully

reviewed the statement of the rejection as well as the cited references and understand the rejection to be based upon Lentini or Young et al. in the alternative and each in combination with Unger and Kataoka et al. Applicants respectfully traverse as follows.

The deficiencies of Lentini, Young et al., and Unger have been described above. Kataoka et al.'s teachings concerning the use of block copolymers to form micelles is alleged to remedy the deficiencies of the other references. As an initial matter, however, Kataoka et al. do not teach any solid support for physical association with a mixture of a photosensitizer and a block copolymer. Therefore, the combination of the references fails to render the claims unpatentable, and the instant rejection should be withdrawn on this basis alone.

Additionally, and assuming for the purposes of argument that a solid support was taught or suggested by the cited references, the teachings of Kataoka et al. are narrower than alleged in the statement of the rejection. On pages 121 through the left column of page 123, Kataoka et al. describe the self assemblage of certain block copolymers into micelles. Importantly, the formation of micelles is by the block copolymers alone. No molecular entity like a drug or photosensitizer is present.

On page 123, right column, through page 129, first paragraph, Kataoka et al. describe the use of an adriamycin-conjugated block copolymer in the preparation and use of micelles composed of the adriamycin portion in the interior of the micelle with the block copolymers on the periphery (see page 127 and Figure 4). Kataoka et al. state on page 123, right column that they "focused on the system by which micelle formation is mainly driven through hydrophobicity and the cohesive force of the conjugated drug itself, because both high loading capacity and high stability can simultaneously be achieved in this system."

*There is no disclosure by Kataoka et al. of micelle formation using a block copolymer that is not conjugated to a (photosensitizer) molecule to be sequestered within a micelle.* The instant claims are not directed to photosensitizers that are conjugated to block copolymer molecules.

Multiple concerns exist with respect to whether and how non-conjugated combinations of block copolymers and a molecule such as a photosensitizer may be formed into micelles. As quoted above, Kataoka et al. used the hydrophobicity of adriamycin itself to stabilize micelle formation by covalently linked adriamycin to the block copolymer. If adriamycin is not

conjugated, then cohesion between adriamycin molecules are not necessarily available to stabilize micelle formation. Instead, intermolecular interactions between adriamycin and the block copolymers would have to be sufficient to allow the production of stable micelles. Kataoka et al. provide no indication that such intermolecular interactions would be enough. The use of a covalent conjugate of adriamycin and block copolymer removes the need to rely on intermolecular interactions between adriamycin and block copolymer.

The artisan of ordinary skill would also be concerned about another concern raised by reliance on intermolecular interactions between block copolymer molecules and a drug or photosensitizer molecule to be sequestered within a micelle. The concern is that it is unknown whether the cohesive forces between the drug or photosensitizer molecules would result in an inner core size that permits intermolecular interactions with block copolymer molecules to form micelles. This is not a concern where the drug or photosensitizer is covalently attached to block copolymer molecules (like in Kataoka et al.) because the latter would always be present by virtue of the covalent bond to the drug or photosensitizer.

The present invention is based in part on the unexpected discovery that non-covalently linked drug or photosensitizer molecules and block copolymer molecules are able to form micelles. Kataoka et al.'s disclosure of a conjugated system provides no reasonable expectation that this combination would result in stable micelle formation.

In light of the above discussion, Applicants respectfully submit that the limitations of the claims are not fully disclosed in the cited references, alone or in combination, and that no reasonable expectation of success exists for a combination of the cited references to result in the instantly claimed invention. Therefore, no *prima facie* case of obviousness exists, and the instant rejection may be properly withdrawn.

***Conclusion***

Applicants believe that the claims are now in condition for allowance and urge early indication to that effect. The Examiner is encouraged to contact the undersigned to expedite prosecution of the instant application.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 27301-20117.00.

Respectfully submitted,

Dated: January 15, 2003 By: _____

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the Claims:**

Kindly amend the claims as follows:

1. (amended) A dried photosensitizer-carrier composition, comprising:

(a) a mixture of at least one photosensitizer and at least one block copolymer carrier agent; and

(b) at least one solid support physically associated with said mixture; wherein said [~~mixture forms liposomes~~] composition forms a complex selected from the group consisting of micelles, vesicles, emulsion, gel and matrix upon hydration with an aqueous medium.

3. (amended) The composition of claim 1 wherein said [~~mixture~~] composition forms, upon hydration with an aqueous based medium, a complex [~~selected from the group consisting of micelles, vesicles, emulsion, gel and matrix~~] that is micellar.

4. (amended) A method for formulating a dried mixture of photosensitizer and carrier agent, comprising the steps of:

(a) mixing together at least one photosensitizer and at least one block copolymer carrier agent in liquid form in contact with at least one solid support; and

(b) physically associating the mixture of photosensitizer and carrier agent with said solid support upon drying said mixture; wherein said mixture forms [~~liposomes~~] a complex selected from the group consisting of micelles, vesicles, emulsion, gel and matrix upon hydration with an aqueous medium.

12. (amended) The composition of claim 11 wherein said porphyrin derivative is selected from the group consisting of green porphyrins, tetrahydrochlorins, [~~(~~]chlorins bacteriochlorins, isobacteriochlorins[~~)~~], pyropheophorphides, purpurins, texaphyrins, phenothiaziniums, phthalocyanines, napthalocyanines, porphycenes and pheophorbides.

15. (amended) The composition [~~or method~~] of claim 14 wherein said BPD ring derivative is selected from a group consisting of benzoporphyrin derivative monoacid ring A (BPD-MA), A-EA6 and A-B3.

17. (amended) The composition [~~or method~~] of claim 16 wherein said endo-support is a polymeric compound.

18. (amended) The method of claim [~~7~~] 16 wherein said endo-support is removed after hydration of the photosensitizer-carrier mixture.

20. (amended) The composition of claim 1 wherein said carrier agent is a [~~block copolymer~~] poloxamer.

21. (amended) The composition of claim 20 wherein said block copolymer carrier is selected from the group consisting of symmetric A-B-A and non-symmetric A-B-A' [~~type~~] triblock copolymers.

22. (amended) The composition [~~or method~~] of claim 21 wherein said triblock copolymer is polyoxyethylene polyoxypropylene block copolymer of the formula [~~HO(C2H4O)a(C3H6O)b(C2H4O)cH~~] $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_cH$, where a and c are independently 1-150 units and b= 10-200 units with the overall molecular weight ranging from 1,000 to 50,000 daltons.

23. (amended) The composition [~~or method~~] of claim 22 wherein said triblock copolymer is selceted from a group consisting of poloxamers wherein a = c = 1 to 150 units and b = 10-200 units

24. (amended) The composition [~~or method~~] of claim 23 wherein said poloxamer is selected from a group consisting of poloxamer 403 (P123), poloxamer 407 (F127), poloxamer 402 (L122), poloxamer 181 (L61), poloxamer 401 (L121), poloxamer 185 (P65), poloxamer 188 (F68) and poloxamer 338 (F108).

25. (amended) The composition [~~or method~~] of claim 24 wherein said poloxamer is selected from a group consisting of poloxamer 181 (L61), poloxamer 401 (L121), and poloxamer 402 (L122).

26. (amended) [~~The~~] A method of preparing a hydrated photosensitizer-carrier complex comprising preparing a dried mixture of photosensitizer and carrier agent by the method of claim 4 [~~further comprising the step of~~] and hydrating said mixture of photosensitizer and carrier agent with an aqueous based medium to produce a hydrated photosensitizer-carrier complex.

27. (amended) The method of claim 26 wherein said complex is [~~selected from a group consisting of micelles, vesicles, emulsion, gel and matrix~~] micellar.

28. (amended) The method of claim [4] 26 wherein said hydrated mixture of photosensitizer, carrier agent, and solid support is [~~hydrated,~~] further processed to a reduced size or further formulated.